REMARKS

Applicants respectfully request reconsideration of the present application in view of the following remarks.

I. Status of the Claims

Claims 1-22 and 25-54 are currently pending in the application, with claims 1, 30 and 35 being the independent claims. Claims 23-24 were previously cancelled without prejudice or disclaimer to the subject matter therein. No claims are amended or added.

II. The Rejection Under 35 U.S.C. § 103(a)

The Office Action, at pages 2-7, rejects claims 1-22 and 25-53 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,573,783 to Desieno *et al.* ("Desieno") and U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge"), in view of U.S. Patent No. 5,811,388 to Friend *et al.* ("Friend"). Applicants respectfully traverse this ground of rejection.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness under 35 U.S.C. § 103. The MPEP § 2142 sets forth the criteria necessary to satisfy this burden:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).*

As discussed below, there is no *prima facie* case of obviousness, because none of these three criteria is satisfied.

A. Summary of the Claimed Invention

The claimed invention is directed to a solid dose *controlled release* nanoparticulate composition comprising a) a nanoparticulate drug composition comprising a poorly soluble nanoparticulate drug and at least one surface stabilizer associated with the surface of the drug, wherein the nanoparticulate drug has an effective average particle size of less than about 1000 nm and at least 50% of the drug particles have an effective average particle size of less than about 1000 nm; and b) at least one *rate-controlling polymer* which is either integrated in a rate-controlling matrix with the drug composition, or coating the nanoparticulate drug composition, wherein *the controlled release nanoparticulate composition provides controlled release of the drug for a time period ranging from 2 to 24 hours.*

The invention is further drawn to a method of preparing the solid dose controlled release nanoparticulate composition, and to a method of treating a mammal comprising administering the formulation.

As stated in the specification, nanoparticulate compositions comprise poorly water-soluble drug particles having an extremely small particle size, i.e., less than one micron. The decrease in particle size and the consequent increase in surface area in the nanoparticulate compositions cause the drug to be rapidly dissolved and absorbed following administration. Thus, the nanoparticulate formulations known in the prior art provide rapid release of drugs. However, while for certain drug formulations rapid release of the drug can be highly desirable, other drug formulations would benefit from a controlled release of the drug to provide therapeutically effective levels of the drug for an extended period of time and a longer period of pharmacologic or diagnostic response as compared to rapid release dosage forms.

The claimed nanoparticulate compositions are specifically designed to prevent rapid dissolution of the drug and *provide controlled drug release by including a rate-controlling*

polymer in the nanoparticulate formulations. The inventors of the present application have made the unexpected discovery that it is possible to formulate *controlled release nanoparticulate compositions that 1) enhance bioavailability of poorly soluble drugs and 2) at the same time extend the release of a drug following administration.*

B. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The primary reference, Desieno, discloses pharmaceutical compositions comprising a carrier particle having on its surface a film comprising nanoparticles of a low solubility drug associated with a steric stabilizer and a film dispersing agent, wherein the film is coated with an overcoating comprising PVP/PEG, and *dissolution of the film results in substantial redispersion of the drug nanoparticles*. *See* col. 2, lines 25-33. Desieno fails to disclose or suggest at least **three** essential elements of the claimed invention. First, Desieno does not disclose or suggest a solid dose *controlled release* nanoparticulate composition. Rather, Desieno contemplates that the drug particles of the invention *provide more rapid onset of the drug action*. *See* col. 8, lines 42-45. In fact, Desieno teaches that the film dispersing agent in the film matrix opposes the binding capability of the film in an aqueous environment, *enhancing film solubility*. *See* col. 4, lines 24-30. Further, Desieno states that the PVP/PEG overcoat provides *improved stability* to the pharmaceutical composition. *See* col. 5, lines 1-4. Second, Desieno fails to teach or suggest a *rate-controlling polymer* integrated in a rate-controlling matrix with the drug composition, or coating the nanoparticulate drug composition. Instead, Desieno discloses polyethylene glycols having average molecular weights in the range of 300 to 8,000, with polyethylene glycol 3350 being the preferred PEG of the invention. *See* col. 5, lines 22-25. While low molecular weight polyethylene glycols, such as Carbowax 3550, are used in the present invention as surface stabilizers (*see* paragraph [0050] in the published application), the claimed controlled release nanoparticulate compositions additionally comprise rate-controlling polymers (which have a high molecular weight), including PEG and PVP. It is well known in the art that polyethylene glycols having low average molecular weight, such as an average molecular weight in the range of 300 to 8,000, cause a fast drug dissolution rate, because the polymer is in a fluid state and maintains

the fluidity of the drug composition when water is imbibed into the drug matrix. High molecular weight polyethylene glycols, high molecular weight PVP, high molecular weight plant exudates or enteric polymers, such as those used in the present application, on the other hand, after imbibing water tend to be viscous and less fluid, thus slowing the drug dissolution rate and providing drug controlled release. *See* also page E5 in Okonogi and Puttipipatkhachorn, *AAPS PharmSciTech 7 (2)*, Article 52 (2006) available at www.aapspharmscitech.org. Third, Desieno fails to teach or suggest a controlled release of the nanoparticulate drug for *a time period of 2 to 24 hours.*

The Office Action recognizes the deficiencies of Desieno. Nevertheless, the Office Action relies on the disclosure of Liversidge for the definition of the phrase "effective average particle size" as including at least 90% of the particles, and on the disclosure of Friend for the teachings of excipients and enteric coating polymers. Neither Liversidge, nor Friend, however, remedy the deficiencies of Desieno.

Liversidge discloses stable drug nanoparticles consisting essentially of a crystalline drug having a surface modifier adsorbed on the surface in an amount sufficient to maintain an effective average particle size of less than about 400 nm. *See* col. 2, lines 30-42. Liversidge makes no mention of controlled release drug formulations. Quite to the contrary, Liversidge states the following:

> It is known that *the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size*. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions.

See col. 1, lines 28-33 (emphasis added).

Thus, *Liversidge teaches against controlled release nanoparticulate compositions*, because Liversidge teaches that the aim of controlling the size and the size range of drug particles is *to increase the rate of dissolution, and thus to increase the release rate of the nanoparticulate drug.* Accordingly, *Liversidge, like Desieno, discloses immediate release*

drug nanoparticulate compositions, and fails to teach or suggest controlled release nanoparticulate compositions.

Friend discloses pharmaceutical compositions for oral administration to preferentially deliver drugs to the lower gastrointestinal (GI) tract, particularly to the colon. *See* col. 1, lines 12-14. Friend specifically teaches that *the compositions and methods of the invention are of a delayed release nature, as compared to sustained or extended release*, and states the following:

> Thus, for purposes of this application *a delayed release composition* allows for the release of most of the active ingredient in the lower GI, particularly the colon without releasing any significant amount of the drug in the upper GI tract as the composition travels through the entire GI tract. *This is different than a sustained release composition that releases the active on a regular (i.e. constant) basis throughout the GI.*

See col. 4, line 66 to col. 5, line 6 (emphasis added). Thus, Friend, like Desieno and Liversidge, fails to teach or suggest controlled release nanoparticulate compositions. In essence, the cited prior art fails to disclose or suggest the unexpected pharmacokinetic properties of the nanoparticle compositions of the present invention.

Furthermore, Applicants state that Desieno and Liversidge are assigned to the same assignee as the present application, namely Elan Pharma International Limited, and are familiar with the disclosures of Desieno and Liversidge. Applicants assert that the nanoparticulate formulations disclosed by Desieno and Liversidge are designed to allow rapid dissolution and release of drugs, as they include only low molecular weight polymers, and do not comprise a rate-controlling high molecular weight polymer.

C. There is no Motivation or Suggestion to Combine the References

The Office Action maintains that Desieno and Liversidge disclose nanoparticulate compositions and infers from these teachings that:

> it would have been obvious for one of ordinary skill in the art to modify the nanoparticle of Desieno and Liversidge using the

> excipients and the enteric coating polymers in an effective amount in view of the teachings of Friend, *because Friend teaches a tablet dosage form suitable for controlled release of poorly soluble drug substance*. The expected result would [sic] *a controlled release film matrix coated carrier that exhibits excellent bioavailability and extremely stable.*

Office Action at page 4 (emphasis added).

This alleged motivation to modify the nanoparticulate compositions disclosed by Desieno and Liversidge into controlled release nanoparticulate compositions, however, is not found in the prior art. As stated above, and contrary to the Office Action's allegation, Liversidge teaches against *controlled release* nanoparticulate compositions. In fact, the goal of Liversidge's invention is to control the size and the size range of drug particles to increase the rate of dissolution, and thus to increase the release rate of the nanoparticulate drug. Friend, on the other hand, teaches that the compositions and methods of the invention are for *delayed release*, **not** for sustained or extended release. Accordingly, the Office Action's alleged motivation is impermissible. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) holds that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not be based on Applicants' disclosure. There must be a motivation to arrive at the presently claimed invention, and clearly such motivation is lacking.

D. One of Skill in the Art Would Have no Expectation of Success

One of skill in the art would not have a reasonable expectation of success in modifying the nanoparticulate compositions of Desieno and Liversidge to provide controlled release nanoparticulate compositions, because, as stated above, the prior art teaches that decreasing drug particle size to nanoparticulate formulations results in a large surface area in relation to volume, and thus cause rapid dissolution and release of the drug after administration. Thus, one of skill in the art would not have known *a priori* whether or not the insertion of a rate-controlling polymer into the nanoparticulate drug matrix or coating layer would a) provide controlled release of the drug; and b) increase bioavailability of the drug.

Accordingly, one of skill in the art would not have a reasonable expectation of success in modifying the references to arrive at the claimed invention.

For at least these reasons, the rejection of claims 1- 22 and 25-54 under 35 U.S.C. § 103(a) is improper. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

Applicants believe that all of the stated grounds of rejections have been properly traversed or rendered moot. Therefore, the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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